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BRIEF REPORT

Consistency of safety profile of new oral anticoagulants in patients with renal failure

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Summary. *Background:* The use of new oral anticoagulants (NOACs) in patients with impaired renal function has raised major concerns, in particular the possibility of an increased risk of bleeding due to accumulation. The aims of this work were to assess the safety of NOACs in patients with renal failure and describe the relationship between clinical events and drug renal excretion magnitude. *Methods:* All phase III trials comparing NOACs with vitamin K antagonists (VKAs) in patients with estimated glomerular filtration (eGFR) rate < 50 mL min^{-1} were eligible. The main safety and efficacy outcomes were major bleeding and thrombosis. A meta-regression was performed to estimate the correlation between the treatment effect estimate and the percentage of renal excretion. *Results:* Nine studies (12 272 patients) were included. A significantly greater relative reduction in major bleeding was seen for NOACs with renal excretion <50% (RR, 0.61; CI, 0.51–0.74) than for those with high renal excretion (RR, 0.96; CI, 0.85–1.07) (interaction test, $P < 0.0001$). A linear relationship between the relative risk of major bleeding and the magnitude of renal excretion was found by meta-regression ($R^2 = 0.66$, $P = 0.03$). For thrombosis, a greater treatment effect of NOA vs. INR-adjusted VKA was observed in patients with eGFR < 50 mL min^{-1} (RR 0.78, CI 0.67–0.92), but no correlation between treatment effect and renal excretion was found. *Conclusions:* New oral anticoagulants were at least as effective as VKAs, with reduced risks of major bleeding and thrombosis in patients with eGFR < 50 mL min^{-1}. The renal excretion of these new drugs seemed to modify the safety profile, contrary to the efficacy.

Keywords: anticoagulants; atrial fibrillation; bleeding; meta-analysis; renal insufficiency; venous thromboembolism.

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Introduction

The efficacy of vitamin K antagonists (VKAs) in the treatment of venous thromboembolism (VTE) and the prevention of stroke in patients with non-valvular atrial fibrillation (NVAF) has been largely described. However, the complex management of this anticoagulant and the risk of iatrogenic events have contributed to the development of new oral anticoagulants (NOACs) that directly inhibit thrombin or factor (F) Xa. New oral anticoagulants have wide therapeutic windows, permitting use of fixed doses without any need for monitoring even in patients with moderate renal failure. They are associated with reduced rates of bleeding in symptomatic VTE [1,2] and intracranial bleeding in NVAF compared with VKAs [3–5].

One-third of outpatients with atrial fibrillation have chronic kidney disease and 15–20% of patients with renal failure have atrial fibrillation [6]. In unselected patients with acute VTE, 6.7% had an estimated glomerular filtration rate (eGFR) between 30 and 60 mL min^{-1} and 5.6% suffered from severe chronic kidney disease (eGFR < 30 mL min^{-1}) [7]. As their renal clearance ranges from 25 to 80%, the use of NOACs in patients with impaired renal function raises major concerns, in particular the possibility of an increased bleeding risk due to accumulation [8]. In fact, the safety profile of dabigatran, which is mostly eliminated by the kidneys, is modified in older patients, a population at risk of renal insufficiency [9]. In the ARISTOTLE trial comparing apixaban, a drug with low renal excretion, with VKA, patients with impaired

renal function seemed to have the greatest reduction in major bleeding with apixaban [10]. However, the subgroup of renal-impaired patients (eGFR < 50 mL min^{-1}) showed a higher incidence of bleeding and thromboembolic events [6,11]. With regards to a hypothetical modification of treatment effects of NOACs according to renal function, we performed a meta-analysis in order to (i) assess the safety of NOACs in patients with moderate or severe renal failure, and (ii) describe the relationship between clinical events and renal excretion magnitude.

Methods

Inclusion criteria

The meta-analysis was performed according to a prospectively developed protocol that prespecified the research objective, the search strategy, the study eligibility criteria, and the methods of data extraction and statistical analysis. All randomized, controlled trials conducted in patients with NVAF and VTE were eligible for inclusion in the present meta-analysis. Patients in the control group had to receive VKAs and patients in the treated group had to receive an oral FXa or thrombin inhibitor. Double-blind and open-label trial designs with or without a blinded evaluation of outcomes were eligible. Studies were excluded if they concerned duplicate cohorts. Trials with short-term follow-ups (< 12 weeks) were excluded.

Data sources and searches

We systematically searched MEDLINE and EMBASE for phase III trials comparing NOACs with VKAs (target INR 2–3) in patients with moderate or severe renal failure (eGFR < 50 mL min^{-1} by the Cockcroft–Gault method) up to October 2013 using sensitive methods and employing the keywords: rivaroxaban, apixaban, betrixaban, edoxaban (DU-176b), eribaxaban, ximelagatran, dabigatran (BIBR1048), LY 517717, darexaban (YM150), letaxaban, AZD0837, TTP889, RB006, MCC977 and TAK442 [12,13]. We also reviewed the citations of the retrieved studies, reviews and meta-analyses obtained by searches of PubMed and Embase. Unpublished and ongoing trials were sought in clinical trial repositories, including those of the National Institute of Health, the National Research Register, Current Controlled Trials, Meta-Embol and Trials Central. We also searched the Internet using the keywords listed above.

When a study was not fully published but an abstract was available, it was included in the meta-analysis if the design had been previously published in detail and the patient characteristics, follow-up and main results had been presented at international congresses. No restrictions with regard to language or sample size were applied. All qualifying studies were assessed for adequate blinding of randomization, completeness of follow-up, and objectivity of the outcome assessment.

Outcomes

The outcomes were (i) major bleeding as defined by the International Society on Thrombosis and Haemostasis [14] and (ii) thrombosis, corresponding to the composite of stroke and systemic embolism, or deep venous thrombosis and pulmonary embolism.

Data extraction

Studies were selected and data extracted from publications by two reviewers independently (JCL and CC). A 2×2 table was constructed for each study to compute the relative risk. If the data required to complete this table were missing or incomplete, the hazard ratio and its confidence interval were extracted and directly included in the pooled results [15]. The risk of bias was assessed by the Cochrane Collaboration's tool [16]. Disagreements were resolved by consensus.

Statistical analysis

Data were analyzed on an intention-to-treat basis. Data were combined for meta-analysis with with EasyMA 2.0 software using the Mantel–Haenszel method to estimate pooled risk ratios (RRs) based on a fixed-effect model [17,18]. Interaction was tested with a threshold of $P < 0.10$ for drugs with high (> 50%) and low (< 50%) renal excretion. The heterogeneity between studies was assessed using Cochran's χ^2 and I^2 [19]. We retained heterogeneity at $P < 0.10$. In the event of unexplained heterogeneity according to drug renal excretion, the results were pooled according to a random-effects model. A meta-regression was performed to estimate the correlation between the treatment effect estimate (i.e. the RR on thrombosis and major bleeding) and the characteristics of the drug studied (expressed as per cent of renal excretion) in order to show if it might influence the size of intervention effect. Studies are weighted by the precision of their respective effect estimate. Results were presented graphically, including the RR and corresponding 95% confidence intervals (95% CIs).

Results and discussion

Description of the studies

Nine trials encompassing 12 272 patients were included, evaluating apixaban (2.5 or 5 mg bid, 3017 and 338 patients in two NVAF and VTE trials) [3,20], rivaroxaban (15 mg od, 2941, 404, and 245 patients in one NVAF and two VTE trials) [1,5], edoxaban (30 mg od, 541 patients in one VTE trial) [2], dabigatran etexilate

(110 or 150 mg bid, 5764 patients in one NVAF trial) [4,21] and ximelagatran (36 mg bid, 1366 patients in 2 NVAF trials) [22]. Their percentage renal clearances were 25%, 33%, 35%, 80% and 80%, respectively. Detailed data for VTE trials with dabigatran [23,24] and one NVAF trial with edoxaban [25] were not available. Patient characteristics, study designs and methodological features are described in Table 1. The mean ages strongly differed between trials testing NOACs in NVAF and venous thromboembolism. Five trials had a double-blind design; four were open-label studies. eGFR was estimated by the Cockcroft–Gault method in all trials. All studies used adjusted-dose warfarin (target INR, 2.0–3.0). The risk of bias according to the Cochrane Collaboration's tool corresponded to the lack of blinding in four trials (Table 2).

Subgroups of patients with renal impairment

Overall, the prevalence of patients with eGFR <50 mL min^{-1} ranged from 7 to 21% in included trials. This co-morbidity was more common in NVAF trials (mean 15%, range 13–21%) than in VTE trials (mean 8%, range 7–12%). The rates of bleeding events for edoxaban were reported only according to the composite criteria encompassing major and clinically relevant non-major hemorrhage [2,14].

Assessment of the impact of drug renal excretion on the efficacy and safety outcomes

Bleeding risk and drug renal excretion The NOACs were associated with a significant reduction of major bleeding (RR, 0.75; CI, 0.59–0.96) in patients with eGFR <50 mL min^{-1}, with a significant heterogeneity ($P = 0.001$, $I^2 = 73\%$) (Fig. 1a). This heterogeneity disappeared when estimating separately the treatment effect for NOACs presenting with an excretion by the kidney > 50% (i.e. dabigatran and ximelagatran [RR, 0.96; CI, 0.85–1.07, $P = 0.58$, $I^2 = 0\%$]) compared with the others (i.e. apixaban, rivaroxaban and edoxaban [RR, 0.61; CI, 0.51–0.74, $P = 0.14$, $I^2 = 42\%$]), with a significant interaction ($P < 0.0001$) between the two subgroups. In Fig. 1(b), the relative risk of major bleeding compared with VKA and its 95% confidence interval were indicated for each drug according to its percentage renal clearance. The pooled reductions in bleeding risk were 48% for apixaban, 26% for rivaroxaban, 27% for edoxaban and 6% for ximelagatran, and there

Table 1 Characteristics of the studies included

Trial, year	Design	NOA class	NOA treatment	Randomization method	ITT	Age	Mean follow-up (months)	Time in therapeutic range (%)
SPORTIF III, 2003	Phase III PROBE	Thrombin inhibitor	Ximelagatran 36 mg bid	Computer-generated and centralized (IVRS)	SSE	70	17.4	66
SPORTIF V, 2005	Phase III Double-blind	Thrombin inhibitor	Ximelagatran 36 mg bid	Computer-generated and centralized (IVRS)	SSE	72	20.0	68
RE-LY, 2009	Phase III PROBE	Thrombin inhibitor	Dabigatran 110 mg bid Dabigatran 150 mg bid	Computer-generated and centralized (IVRS)	All outcomes	71	24.0	64
ROCKET-AF, 2011	Phase III Double-blind	Factor Xa inhibitor	Rivaroxaban 15 mg od	Computer-generated and centralized (IVRS)	SSE	73	23.2	55
ARISTOTLE, 2011	Phase III Double-blind	Factor Xa inhibitor	Apixaban 2.5 mg bid	Computer-generated and centralized (IVRS) – stratification according to investigative site and prior VKA status	All outcomes	70	21.6	62
EISNTEIN-DVT, 2010 EINSTEIN-PE, 2012	Phase III PROBE	Factor Xa inhibitor	Rivaroxaban 15 mg bid for 3 weeks, followed by 20 mg od	Computer-generated and centralized (IVRS)	PE and DVT	57	6.7	62
AMPLIFY, 2013	Phase III Double-blind	Factor Xa inhibitor	Apixaban 10 mg bid for 7 days, 5 mg bid for 6 months	Computer-generated and centralized (IVRS) – stratification according to DVT or PE	PE and DVT	57	NR	61
HOKUSAI, 2013	Phase III Double-blind	Factor Xa inhibitor	Edoxaban 30 mg od after 5 days of heparins		All outcomes	56	8.5	64

Bid, twice daily; ITT, intention-to-treat analysis; IVRS, interactive voice-response system; NR, not reported; od, once daily; PROBE, prospective, randomized, open, blinded-endpoint; SSE, stroke and systemic embolism.

Table 2 Assessment of the risk of bias according to the Cochrane Collaboration's tool

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
SPORTIF III, 2003	+	+	–	+	+	+
SPORTIF V, 2005	+	+	+	+	+	+
RE-LY, 2009	+	+	–	+	+	+
EINSTEIN-DVT, 2010	+	+	–	+	+	+
ROCKET-AF, 2011	+	+	+	+	+	+
ARISTOTLE, 2011	+	+	+	+	+	+
EINSTEIN-PE, 2012	+	+	–	+	+	+
AMPLIFY, 2013	+	+	+	+	+	+
HOKUSAI, 2013	+	+	+	+	+	+

+, low risk of bias; –, high risk of bias.

was an increase of 1% for dabigatran, following the same order as their percentage renal clearances: 25%, 33%, 35%, 80% and 80%, respectively. A linear relationship between the relative risk of major bleeding and the magnitude of renal excretion was found ($R^2 = 0.66$, $P = 0.03$ by meta-regression). No correlation was retained between renal drug excretion and stroke reduction.

After the removal of the HOKUSAI trial, the results of the meta-analysis restricted to major bleeding were unchanged: NOACs significantly reduced the risk of major bleeding with a significant interaction ($P = 0.01$) between drugs with low (RR, 0.57; CI, 0.39–0.85) and high (0.96; CI, 0.85–1.07) renal excretion. The meta-regression provided similar results ($R^2 = 0.66$) with a statistical trend towards significance ($P = 0.06$).

Thrombosis and drug renal excretion A significant reduction of thrombosis by NOACs compared with standard treatment was found (RR, 0.78; CI, 0.67–0.92; $P = 0.004$) without heterogeneity across trials ($P = 0.36$, $I^2 = 9\%$) (Fig. 2a). No interaction was retained for this outcome ($P = 0.43$) when considering drugs mainly excreted by the kidneys (> 50%) vs. the others. We found no correlation (Fig. 2b) between the renal excretion of NOACs and the reduction of thrombotic events by NOACs compared with VKA by metaregression ($P = 0.59$).

This meta-analysis summarized the available data concerning the treatment effect of NOACs in patients with moderate or severe renal failure. New oral anticoagulants were at least as efficacious as warfarin, with reduced risks of major bleeding and thrombosis in patients with eGFR < 50 mL min^{-1}. It should be noted that such an effect was obtained with the use of a reduced dose for apixaban, edoxaban and rivaroxaban in patients with eGFR < 50 mL min^{-1}. Most importantly, we reported a linear correlation between major bleeding and the extent of drug renal excretion that divided NOACs into two groups: a group with a renal excretion < 50% with a significant 39% reduction of bleeding, and a group with a high renal excretion with no difference in bleeding compared with VKA. Even though the safety profile of NOACs as a whole remains comparable to VKA in these patients, NOACs with a low renal clearance might be preferred according to the results of this meta-analysis, especially because the level of renal excretion seemed to have no impact on the reduction of thrombotic events. These assumptions were strengthened by the recent publication ENGAGE AF-TIMI 48, a phase III trial assessing edoxaban (15 or 30 mg od) with a dose reduced by half in the case of eGFR < 50 mL min^{-1} in NVAF [25]. As reported in the forest plot of the appendix (the numeric values were not available), edoxaban significantly reduced the risk of bleeding by nearly 40% for the dose of 7.5 mg day^{-1} and 70% for the dose of 15 mg day^{-1} compared with warfarin, with an interaction ($P < 0.05$) between the different levels of eGFR for the two doses. The treatment effect of edoxaban and warfarin did not differ for stroke and systolic embolism.

However, our study suffered from several limitations that might restrict the impact of our findings. First, our meta-analysis is a combination of subgroups with a *post hoc* analysis, and the trials were not designed to assess the treatment effect of NOACs in patients with renal failure. However, the analysis of pooled populations was an opportunity to increase statistical power and detect significant differences. Second, the limitations of indirect comparison did not permit firm recommendations to physicians likely to prescribe NOACs; our meta-analysis should be viewed as a hypothesis-generation study. In fact, the design and patient characteristics of the included studies notably differed, especially between the two indications of NOACs (i.e. NVAF and venous thromboembolism).

The benefit-risk balance seemed to be favorable for this new pharmacologic class in the case of eGFR < 50 mL min^{-1}, with a significant global reduction of thrombosis. The renal excretion drugs might modify the safety profile, contrary to the efficacy of these new drugs. The publication of the results of the RE-MEDY and RESONATE trials comparing dabigatran with standard ther-

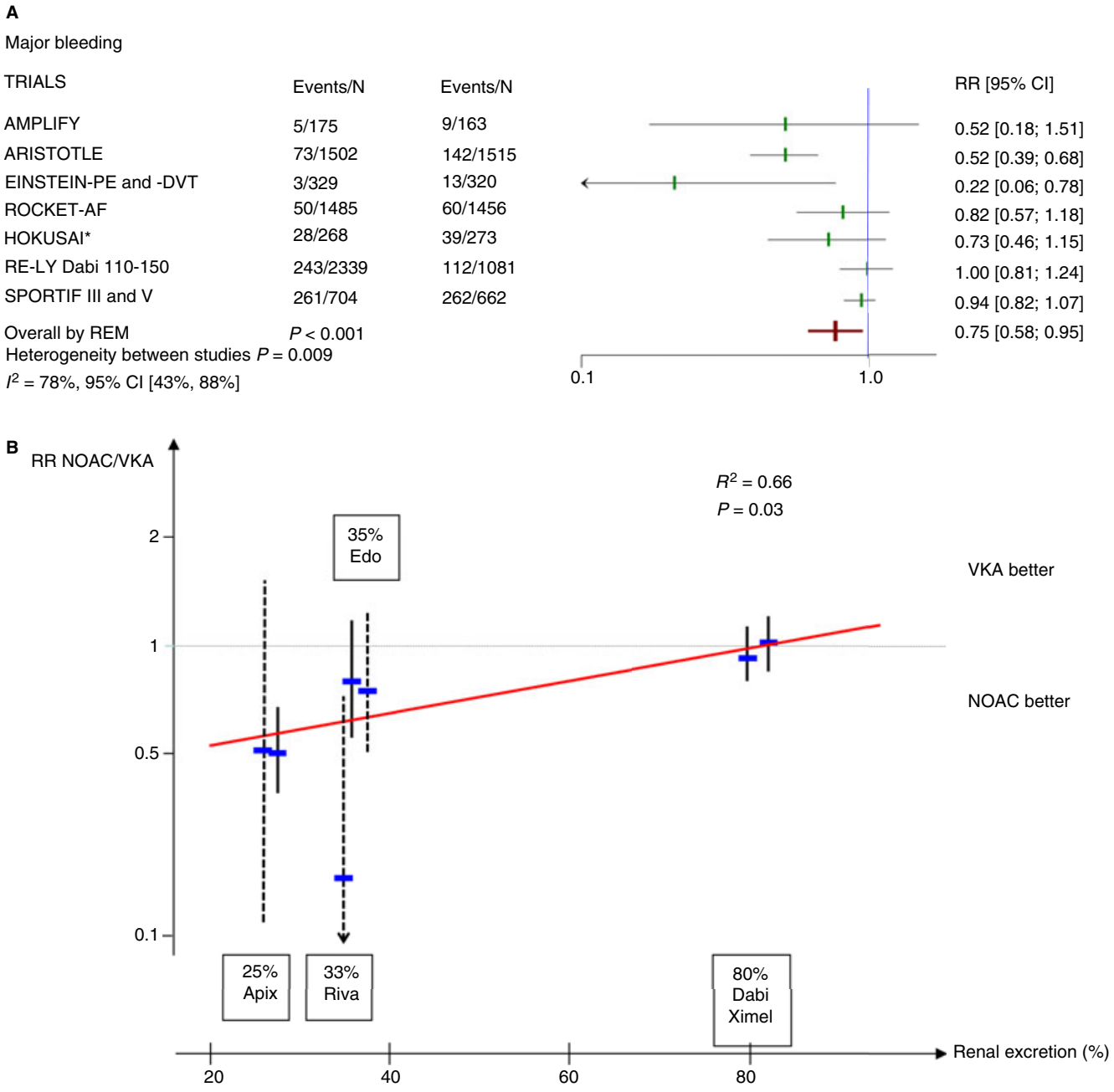

Fig. 1. Meta-analysis (A) of the effect of new oral anticoagulants on major bleeding in patients with estimated glomerular filtration rate <50 mL min^{-1}. Metaregression (B) of relative risk of major bleeding with new oral anticoagulants (major and clinically relevant non-major hemorrhage for edoxaban) compared with VKAs in patients with moderate or severe renal impairment (*y*-axis) according to percentage renal excretion (*x*-axis). The results for dabigatran etexilate 110 and 150 mg and ximelagatran reported in the SPORTIF III and V trials were pooled. The results of venous thromboembolism trials are in dotted lines. Apix, apixaban; Dabi, dabigatran; Edo, edoxaban; *N*, number of patients in each arm; NOAC, new oral anticoagulant; Riva, rivaroxaban; REM, random-effects model; RR, relative risk; VKA, vitamin K antagonist; Ximel, ximelagatran. *Major bleeding and clinically relevant non-major bleeding were pooled in the HOKUSAI trial

apy for patients with renal impairment [23,24] should permit validation of our hypothesis.

Addendum

J.-C. Lega, L. Bertoletti and S. Laporte designed the study. J.-C. Lega, L. Bertolettio, C. Boissier and C. Gremillet contributed to acquisition of data. J.-C. Lega and S. Laporte were responsible for the statistical analyses. J.-C. Lega, P. Mismetti and L. Bertoletti interpreted data. J.-C. Lega, L. Bertoletti, and C. Gremillet planned and wrote the first draft of the paper, which was subsequently revised by all authors. All authors read and approved the final manuscript. J.-C. Lega is guarantor.

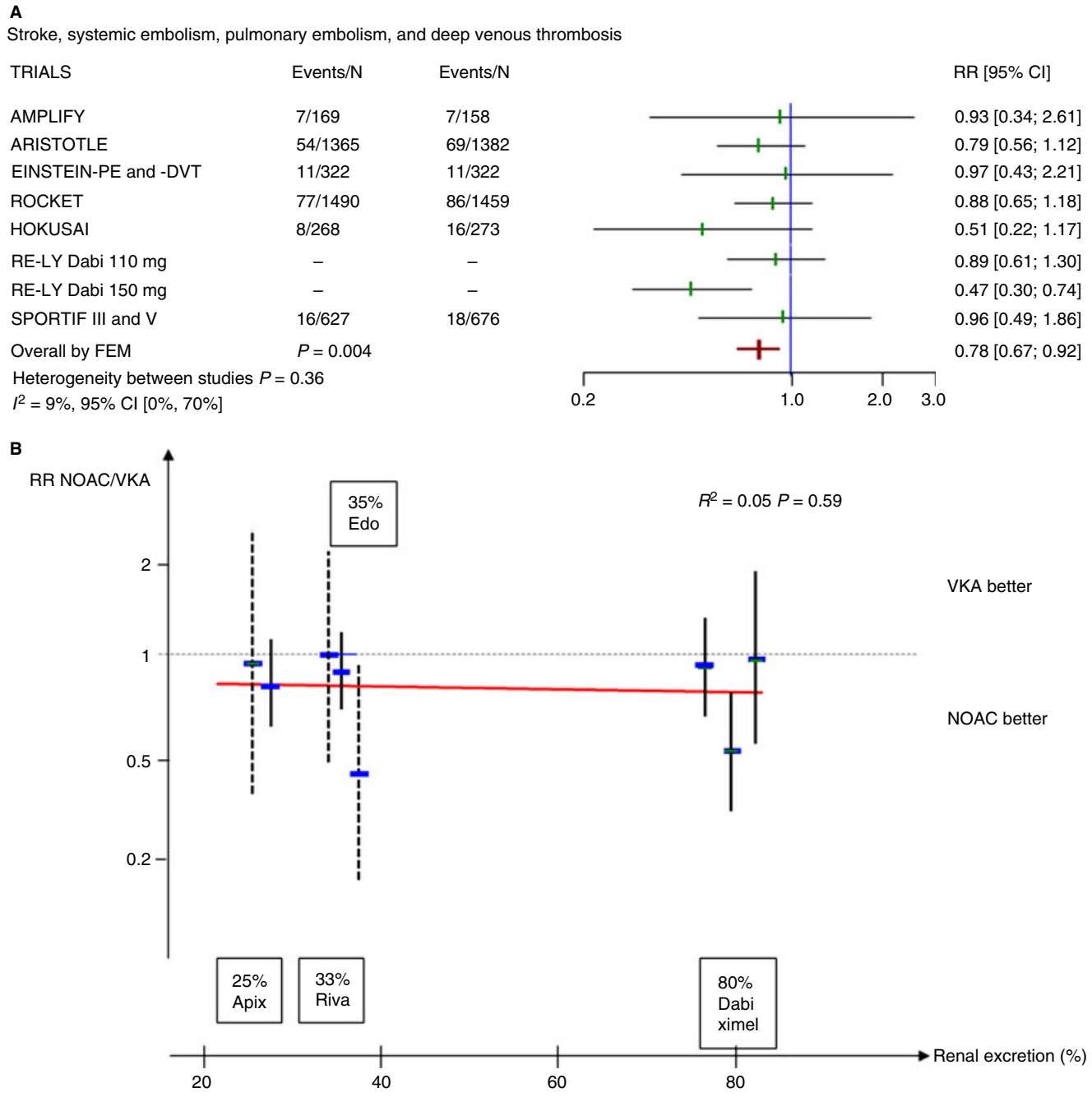

Fig. 2. Meta-analysis (A) of the effect of new oral anticoagulants on thrombotic events in patients with estimated glomerular filtration rate <50 mL min^{-1}. Metaregression (B) of relative risk of thrombosis with new oral anticoagulants compared with VKAs in patients with moderate or severe renal impairment (*y*-axis) according to percentage renal excretion (*x*-axis). The results for ximelagatran reported in the SPORTIF III and V trials were pooled. The results of venous thromboembolism trials are in dotted lines. Apix, apixaban; Dabi, dabigatran; Edo, edoxaban; FEM, fixed-effects model; *N*, number of patients in each arm; NOAC, new oral anticoagulant; Riva, rivaroxaban; RR, relative risk; VKA, vitamin K antagonist; Ximel, ximelagatran.

Disclosure of Conflict of Interests

J-C. Lega, P. Mismetti, L. Bertoletti, S. Laporte, C. Boissier and C. Gremillet received no direct support for this study; S. Laporte received support from the Ministère de la Recherche through a Programme Hospital de Recherche Clinique grant in 2008 (Meta-Embol). P. Mismetti and S. Laporte sit on an advisory board for Boehringer Ingelheim, BMS/Pfizer and Bayer, and Daichii Sankyo for P. Mismetti. P. Mismetti has received honorariums from Sanofi-Aventis, GSK, Astra Zeneca, Merck Serono, Boehringer Ingelheim and Bayer; S. Laporte has received honorariums from Sanofi-Aventis, Merck Serono, Boehringer Ingelheim and Bayer. There are no other relation-

ships or activities that could appear to have influenced the submitted work.

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